fundamental aspects of the American way of doing things. How things work out will indeed be a test of how Americans do things. It is to be hoped that the aims of the law can be achieved. Quality assurance and cost containment in medical care are goals shared by all concerned. Ideally there can be a true partnership between government and the private sector. Ideally the problems and conflicts can be resolved by persons of good will, without undue use of force on the one hand or resort to the courts on the other. There is much at stake in this largely uncharted area of professional and public interaction. So far the program is apparently being implemented slowly and on the whole wisely—and this is about all that can be expected at this time.

—MSMW

Rickets

THAT A specialty conference on rickets (such as appears elsewhere in this issue) should command interest in 1976 is in itself a matter worthy of comment. In the 1950's it was generally held that everything worth knowing about rickets had been learned. An ancient disease which had become a major affliction of infants and children in the industrial cities of northern Europe and the United States during the 19th and early 20th centuries had at last been conquered.[1] The consequences of rickets in childhood were not only the hypocalcemic tetany and the visible deformities of head, chest, spine and legs of the severely rachitic child, but also the hidden deformity of the pelvis which in the female was a major cause of dystocia and almost certainly of maternal and infant mortality and morbidity.

Following development of an animal model for rickets in 1918 there followed quickly the identification of an antirachitic factor in cod liver oil separate from the already known vitamin A in this odoriferous and rather unpleasant tasting folk remedy for rickets. The relationship of ultraviolet energy to vitamin D was also soon learned, leading to the development of a laboratory process for production of concentrated preparations of vitamin D by irradiation of ergosterol—a plant sterol—or 7-dehydrocholesterol—the sterol from which the natural vitamin D is produced in the skin of man—by exposure to short wave ultraviolet radiation. These concentrated preparations of vitamin D were inexpensive to prepare and could be added without difficulty to evaporated milk, homogenized pasteurized milk or the special infant feeds based on cow's milk whey. Since this fortification of cow's milk with vitamin D coincided with the trend away from breast feeding the result was that most infants automatically received enough vitamin D without the necessity for the mother to add vitamin preparations or to attempt to expose the infant's skin to sunshine, which would not be helpful anyway in winter months in northern latitudes. The importance of skin exposure to sunshine as a source of vitamin D is emphasized by the low vitamin D content of human milk so that breast-fed infants not given vitamin D are at risk for rickets—as illustrated by Case 3 presented in this month's specialty conference.

By 1950, vitamin D deficiency rickets had become an uncommon disease instead of an everyday problem. At that time it seemed that further research on vitamin D might provide theoretical information of interest but was not likely to have practical application in the treatment of patients. Research did continue, however, because of the desire to understand the physiologic basis of the action of this highly potent agent of which only a few micrograms a day were sufficient to prevent rickets.

Investigators of the physiology of vitamin D took advantage of new techniques for the study of calcium homeostasis. One was the use of isotopic calcium, which simplified investigation of calcium absorption from the intestine[2] and made possible the study of calcium turnover in the skeleton, so called calcium kinetics. Of great value was the adaptation to the study of intestinal calcium transport of a method devised by gastrointestinal physiologists for examining intestinal absorption of organic solutes such as glucose and amino acids. This was the everted intestinal preparation, an *in vitro* system that could be used for measuring net mucosal to serosal transport of calcium.[3,4]

It was quickly found that such transport was much greater in preparations from rats treated with vitamin D than from vitamin D depleted animals. It was also learned that vitamin D had to be given to the animal at least several hours before the intestine was removed for the *in vitro* study even when very large doses of vitamin D were fed. The basis of this lag period then became the subject of intensive study. Two theories were developed: (1) that the vitamin had to be transformed metabolically into an active principle by tissues other than the intestine and (2) that vitamin D acted in the intestinal mucosal cells to induce synthesis of a protein or proteins which functioned to facilitate transport of calcium and of phosphate. Both theories proved to be correct. Evidence was developed that vitamin D did activate DNA-mediated mRNA synthesis and induce the synthesis of at least one specific intestinal cell protein characterized by its ability to complex calcium and called calcium binding protein (CABP).[5]

At the same time, the studies by DeLuca and his colleagues indicated that vitamin D was hydroxylated in the liver to 25-OH vitamin D which stimulated calcium transport by the everted intestinal preparation with a shorter lag period than did vitamin D.[6] Results of studies by Norman and also Kodicek[7] indicated, however, that the compound which complexed with the nuclear chromatin of the intestinal mucosal cell was not 25-OH vitamin D. A further metabolite of 25-OH vitamin D (1,25-di OH vitamin D) was discovered that is the presumed active vitamin D hormone.[8] The extraordinarily interesting fact about this compound is that the kidney is the only site of its production. There is thus a complex cycle of vitamin D metabolism with an initial hydroxylation by a liver microsomal system and a second hydroxylation by a kidney mitochondrial system.

The latter system is controlled by a feedback mechanism that adjusts the production of the vitamin D hormone to the concentrations of calcium and phosphate in body fluids. The formation of 1,25-di OH vitamin D is stimulated by parathyroid hormone and by a low concentration of inorganic phosphate. Calcium deficiency resulting from a low calcium diet stimulates parathyroid hormone output which in turn increases the formation of 1,25-di OH vitamin D which operates to increase the efficiency of calcium absorption. Hypophosphatemia also stimulates 1,25-di OH vitamin D production. This compound functions to increase both phosphate transport in the intestine and also renal tubular reabsorption of phosphate as an adaptive function. The interrelationship between parathyroid hormone and vitamin D is complex in that not only is parathyroid hormone needed for adequate formation of 1,25-di OH vitamin D but vitamin D is required for the full action of parathyroid hormone. Hypocalcemia with convulsions is, therefore, an important early manifestation of vitamin D deficiency (Cases 2 and 3 in the specialty conference).

By chance the elucidation of the vitamin D cycle coincided with the development of new thoughts about the treatment of chronic progressive renal disease including not only diet but aggressive measures to replace the defective kidney function such as dialysis and renal transplant. It was now possible to understand the calcium malabsorption and secondary hyperparathyroidism of kidney failure in terms of deficiency of 1,25-di OH vitamin D resulting from the reduced metabolic mass of kidney tissue and also the hyperphosphatemia secondary to glomerular insufficiency. With this understanding have come better methods for preventing this secondary hyperparathyroidism and the consequent skeletal demineralization and painful deformity which incapacitated patients with severe kidney insufficiency.

Vitamin D deficiency rickets is an uncommon problem today but forms of rickets are encountered that are not prevented by administering ordinary amounts of vitamin D. These vitamin D resistant varieties of rickets can now be classified and treated more effectively by virtue of better understanding of the metabolism and mechanism of action of vitamin D.[9] The hypocalcemia and rickets of infants with neonatal hepatitis or chronic obstructive jaundice is at least in part due to failure of 25-hydroxylation of vitamin D by the liver, which is a necessary step in the formation of 1,25-di OH vitamin D. Treatment of such patients with 25-OH vitamin D is effective.

The rickets and osteomalacia sometimes seen in patients with seizure disorders who are receiving treatment with anticonvulsant drugs[10] are possibly due to accelerated vitamin D metabolism and inactivation by glycuronidation, resulting from induction of hepatic enzyme activity by such drugs as phenobarbital and phenytoin. Study of this problem has been made possible by methods for determining the 25-OH vitamin D level in the serum based on the binding of this compound by receptors in kidney cytosol or binding proteins in rat serum. Although serum 25-OH vitamin D concentrations are reduced by treatment with anticonvulsant drugs, this may not be the sole action of these drugs and there is some evidence of a direct effect on calcium transport by the intestine. Because of the large numbers of children and adults receiving anticonvulsant drugs it is important to study this problem further.

There are forms of rickets, so-called vitamin D dependent rickets or where there is an increased requirement of vitamin D, that are the result of an inborn error of metabolism of vitamin D which may be a defect in the control of the 1-hydroxylation system in the kidney. The patient in Case 1, in whom more than the usual amount of vitamin D apparently was required to prevent rickets but in whom rickets healed after administration of 10,000 units of vitamin D per day, may represent a mild variant of this metabolic disorder. The family history supports a genetic basis for this problem.

It has been disappointing but not surprising to discover that the most common variety of rickets that is not preventable by vitamin D administration—that is, primary hypophosphatemic rickets —cannot be ascribed to a defect in the vitamin D cycle. The mechanism remains a matter of argument and various theories have been proposed, such as absence of a renal tubular transport system for phosphate other than that controlled by parathyroid hormone,[11] hyperresponsiveness to parathyroid hormone in physiologic concentration with inhibition of phosphate transport[12] and target cell refractoriness to 1,25-di OH vitamin D resulting in deficiency of calcium and phosphate absorption by the intestine and impaired tubular reabsorption of phosphate.[13] An even more speculative possibility has also been considered: that there may be a circulating humoral factor other than parathyroid hormone that inhibits tubular reabsorption of phosphate.[14] There is genetic heterogeneity of primary hypophosphatemia since a phenotypically identical disorder has been found in kindreds in whom the inheritance is through a dominant gene on the X-chromosome, an autosomal dominant gene and an autosomal recessive gene. Possibly there is heterogeneity of the physiologic defect also. Certainly there are pronounced differences among patients in the severity of the process which cannot be entirely explained by X-linked inheritance and the Lyons hypothesis. Despite differences of opinion concerning the physiologic defect there is agreement that megadoses of vitamin D are not curative and can be nephrotoxic. Treatment has therefore been altered to depend more on high phosphate intake in the form of a buffered solution of sodium and potassium phosphates to raise serum phosphate, with only enough vitamin D or dihydrotachysterol to maintain adequate calcium absorption and block parathyroid hormone secretion.

The history of rickets research should remind us—and such reminders may be necessary—that physiologic and biochemical research directed at understanding as completely as possible both the normal and the altered physiologic processes of disease provides not only satisfaction to scientists but benefits to people generally in the form of more effective prevention and treatment of disease.

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